REMARKS

Claim 20 remains in the application. Claim 20 is the only claim in independent form. The present claim has been amended in order to further clarify the present invention and place the application in condition for allowance.

Claim 20 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action holds that the claim is unclear because there is no positive, active method step of detecting or identifying any marker that is indicative of early stage cancer. In response thereto, Applicants have amended claim 20 to indicate that the epitope bearing clones in the "identifying step" are markers indicative of early stage cancer.

The Office Action further holds that the claim is unclear because if the patients are already known to have cancer, clarification is needed of what is indicative of early stage cancer. In response thereto, Applicants point out that the method of detecting and identifying markers indicative of early stage cancer requires the analysis and reaction with antibodies of serum of patients that are already known to have cancer in order to identify epitopes (i.e. markers) that can be used to indicate early stage cancer in other patients upon whom the protein array assay will be performed. See page 25 of the specification:

> "In order to develop an effective screening test for early detection of ovarian cancer, cDNA phage display libraries are used to isolate cDNAs coding for epitopes reacting with antibodies present specifically in the sera of patients with ovarian cancer. The methods of the present invention detect various antibodies that are produced by patients in reaction to proteins expressed in their ovarian tumors. This is achievable by differential biopanning technology using human sera collected both from normal individuals and patients having ovarian cancer and phage display libraries expressing cDNAs of genes expressed in ovarian epithelial tumors and cell lines. Serum reactivity toward a cellular protein can occur because of the presentation to the immune system of a mutated form of the protein from the tumor cells or

> overexpression of the protein in the tumor cells. The strategy provides for the identification of epitope-bearing phage clones (phagotopes) displaying reactivity with antibodies present in sera of patients having ovarian cancer but not in control sera from unaffected women. This strategy leads to the identification of novel disease-related epitopes for diseases including, but not limited to ovarian cancer, that have prognostic/diagnostic value with additional potential for therapeutic vaccines and medical imaging reagents. This also creates a database which can be used to determine both the presence of disease and the stage of the disease.
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> The series of experiments disclosed herein provide direct evidence that biopanning a T7 coat protein fusion library can isolate epitopes for antibodies present in polyclonal sera. This also showed that the technology can be applied to direct microarray screening of large numbers of selected phage against numerous patient and control sera. This approach provides a large number of biomarkers for early detection of disease."

In other words, the patients who already have cancer are used to create the protein array assay, whereas the protein array assay will be used with patients who are unknown to have cancer in order to detect early stage cancer. Thus, the claim is clear.

The Office Action further holds that the phrase "including all epitopes identified in protein array assays for detecting early stage cancer" is unclear because no protein array assays were performed in previous steps. In response thereto, Applicants have amended the claim to read "including all identified epitopes in a protein array assay designed to detect early stage cancer" as suggested by the Office Action.

Reconsideration of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claim 20 stands rejected under 35 U.S.C. §103(b) as being unpatentable over Sioud, et al. The Office Action holds that Sioud, et al. teaches the analysis of the humoral response in patients with cancer; libraries from breast cancer cell lines were biopanned and positive clones were selected; using serum antibodies from patients with breast cancer, IgG-binding phage-encoded cDNA products

were selected and the clones identified important antigens including p53, pentraxin and others; and the selected phage-displayed cDNA products were recognized by a significant number of breast cancer sera as compared to normal individuals.

More specifically, it is undisputed that the primary reference, the Sioud, et al., reference, discloses the step of biopanning libraries for selecting phage display cDNA products recognized by a significant number of breast cancer sera as compared to sera from normal individuals. The Sioud, et al., reference concluded that "the obtained results demonstrate that phage display could be a valuable method for the identification of antigens recognized by the humoral immune system in patients with cancer." (Sioud, et al., reference, abstract).

As previously argued by Applicants, it is admitted that it is well-known to biopan for a specific composition, as disclosed in the Sioud, et al., reference. That is, the Sioud, et al., reference discloses biopanning methods aimed at determining the presence of a single significant marker. There is no disclosure or suggestion in the Sioud, et al., reference of a method or assay that simultaneously screens for an unlimited number of markers within sera. The cited reference only teaches obtaining approximately five to ten markers. This is known in the art to be a low throughput method. This is consistent with the commonly accepted convention of determining a single marker for diagnostic purposes, such as those used for prostate cancer, breast cancer, or the like. Moreover, the methodology disclosed in the Sioud, et al., reference teaches away from the use of a large array, or more specifically, including all epitopes uncovered during biopanning related to a disease, because the primary goal, as disclosed in the first full paragraph of page 718 of the Sioud, et al., reference is to ". . . enrich for the best binders. If the selection is specific an increase in the number of positive clones is likely." The additional selections disclosed in the Sioud, et al., reference were designed to increase the specificity for finding a few highly specific markers. Identifying ***all*** epitopes in the present invention and therefore requiring a large protein array is certainly not the same as identifying ***five to ten*** markers as in

Sioud, et al. Applicants have further amended claim 20 to require that all the epitopes identified are included on a ***microarray***, which Sioud, et al. neither discloses nor suggests. This amendment has numerous support throughout the specification, for example page 25 cited above.

The present invention provides unexpected results in view of the convention of the prior art. The present invention, as set forth in independent claim 20, is characterized by identifying ***all epitope-bearing clones*** that are specific to early-stage cancer and including ***all epitopes identified*** in protein arrays for detecting early-stage cancer. This teaching goes directly against the teachings of all the cited prior art. Moreover, as discussed previously during the personal interview, the present invention as set forth in pending claim 20 provides unexpected results by providing a broad range, yet sensitive assay, capable of detecting early-stage cancer, as supported on page 42 of the presently pending patent application. The present invention provides a method of identifying and detecting markers indicative of early-stage cancer, thereby allowing the practitioner to utilize more specific diagnostic procedures to confirm the early-stage cancer and then prescribe early-stage treatments. The prior art does not provide markers nor does it even suggest the provision of markers for such early-stage detection of cancer. Treatment of early-stage cancer is known to be significantly more effective than treatment of later-stage cancer. Hence, the present invention provides unexpected results not obtained by the prior art. That is, the present invention includes all epitopes identified in protein array assays for detecting early-stage cancer. Such unexpected results overcome a *prima facie* obviousness-type rejection as a matter of law. Hence, it is respectfully submitted that independent claim 20 is patentable over the cited prior art.

The remaining dependent claims not discussed above are ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior art reference discloses or suggests the invention as set forth in the claims as discussed in detail above.

In conclusion, it is respectfully submitted that the presently pending claims are in condition for allowance, which allowance is respectfully requested. Applicant respectfully requests to be contacted by telephone if any remaining issues exist.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Connie Herty